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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,399	11/04/2002	Barry L. Stoddard	14538A5310US	7642

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EXAMINER	
NASHED, NASHAAT T	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 07/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,399	STODDARD ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-6 and 11-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4-6, and 11-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

The application has been amended as requested in the communication filed May 9, 2005. Accordingly, claims 3, and 8-10 have been cancelled.

Claims 1, 2, 4-6 and 11-15 are pending and under consideration.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Although the Figure description of Figure 2 indicates that the sequences in the figure are SEQ ID NO: 7 through SEQ ID NO: 12, the sequences in the Figures are not associated with a specific sequence identification number in the Figure or the Figure description. The amino acid residues referenced throughout in the specification are from an amino acid sequence disclosed in the specification and the sequence from which they are, should be identified at each occurrence, see for example the figure description of Figure 4-6. Since human factor VIII amino acid sequence is disclosed in the specification, each time the protein is mentioned in the specification, it should be identified by its sequence identification number at each occurrence, see for example page 10, line 5.

The indicated allowability of claims 1-2, 4-6, and 11-15 in the previous Office action mailed November 4, 2004 has been withdrawn in order to present the following rejections.

> The following is a quotation of the first paragraph of 35 U.S.C. 112:
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-6, and 11-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 4-6, and 11-15 are directed to all possible crystals of a complex comprising of any N-terminal truncated factor VIII from any biological or man-made source and any ligand wherein said N-terminal truncated factor VIII lacks at least 2000 amino acid residue of the full length factor VIII. The specification, however, only

provides a single representative species of these crystals which appears to be orthorhombic crystal of residues 2169-2332 of human factor VIII of SEQ ID NO: 1 wherein Val mutant at position 2169 and Cys mutation at position 2296 in space group $P2_12_12_1$ having unit cell dimension a = 46, b = 57, and c = 66 Angstrom units. There is no disclosure of any particular relationship between the amino acid sequence of the protein and/or the ligand of the binary complex and the crystallization conditions. The specification also fails to describe additional representative species of these crystals by any identifying structural characteristics or properties other than the space group and cell dimension cited in claim 5, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims 1, 2, 4-6, and 11-15 are directed to a method of obtaining any crystal of said ternary complex under any crystallization conditions, which include the crystallization of any ternary complex as cited above using any precipitant, at any pH, in any buffer system, at any protein concentration and temperature. The specification, however, only provides a single representative species of these crystallization conditions at page 136, lines 3-11. There is no disclosure of any particular relationship between the structure of the ternary complex and the crystallization conditions. The specification also fails to describe additional representative species of these crystallization conditions by any identifying compositions or properties other than those cell dimension cited in claim 9, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims 1, 2, 4-6, and 11-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to all-possible crystals comprising a binary complex consisting of any N-terminal truncated VIII which lacks at least 2000 amino acid residues from any biological source and mutants thereof glycosylated or non-glycosylated and any ligand and any method of using said crystal in drug screening assay and method of obtaining said crystal. Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the

invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses any method to obtain any crystal comprising a binary complex consisting of any N-terminally truncated factor VIII from any biological or man-made source in which lacks at least residues 1-2000 from the N-terminus glycosylated or non-glycosylated and any ligand which may include a another protein or a small molecule, any crystal product of said method, and any method of using said crystal in drug screening assay. The specification provides guidance and examples in the form of an assay appears to identify a specific mutant protein consisting of residues 2169-2332 of human factor VIII of SEQ ID NO: 1 wherein Val mutant at position 2169 and Cys mutation at position 2296. Said specific protein crystallized under specific crystallization condition in what appears to be an orthorhombic crystal in space group $P2_12_12_1$ having unit cell dimension a = 46, b = 57, and c = 66 Angstrom units, see page 32, last paragraph. The examiner would like to admit his confusion at this junction becuase the specification teaches different samples of the crystal display "non-isomorphism". The examiner does not understand the meaning of non-isomorphism. Isomorphous crystals are required of the crystal for the successful determination of the three-dimensional structure. If they could not obtain isomorphous crystal they could not have obtain the structure, and therefore, the claims lack enablement in the specification. It is not clear from the application or applicants' publication (Pratt *et al.* Nature Vol. 402, 11/1999, pages 439-442) how applicants over come this problem. In addition, the crystallized protein consists of residue 2171-2332 of human factor VIII, which contained the cysteine to valine substitution at the N-terminus of the truncated protein and substitution serine-2296 with cysteine. Otherwise the application and the publication appear to have the same Tables and results. While molecular biological techniques and genetic manipulation to make any N-terminally truncated factor VIII protein from any biological source in a glycosylated or non-glycosylated form are known in the prior art and the skill of the artisan are well developed, knowledge regarding crystallization of proteins and their complexes is lacking. It is well established in the art that obtaining a protein and its complexes in a crystal form crystallizing is highly unpredictable. The specification itself describes several failures in obtaining the desired crystal. The skilled artesian would be expected to screen large number of crystallization conditions, which may include screening variety of conditions in space, a micro gravity environment. A protein which may crystallize under specific crystallization condition, it mutants may or may not crystallize under the same condition. In many cases, a protein that can't be crystallized, one of its specific mutants might be crystallizable. It should be noted that applicant obtained a crystal of a specific truncated double mutants. Even if a crystal is obtained, it may or may not be suitable for structure determination by X-ray crystallography. Thus, searching for a crystallization conditions for a protein and its complexes that is suitable for X-ray crystallography is well outside the realm of routine experimentation and predictability in the art of success in is extremely low. The amount of experimentation to identify a crystallizable factor VIII fragment glycosylated or unglycosylated, its

cystallizable mutants, a lignad for said truncated factor VIII, and identify a crystal suitable for structure determination X-ray crystallography is enormous. Since routine experimentation in the art does not include screening large number of crystallization condition or mutants which can be crystallized where the expectation of obtaining the desired crystal is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the specific amino acid sequence of the truncated factor VIII, the chemical structure of ligand, and the crystallization conditions that produce a crystal suitable for structure determination by X-ray crystallography. Without such guidance, the experimentation left to those skilled in the art is undue.

> The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 11 and 12 are provides for the use of a crystal, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 11 and 12 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on TWTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen M. Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit 1656